REMARKS

Applicants thank the Examiner for the courtesy extended in the interview with Applicants' Attorney on April 27, 2004.

The instant Application was filed on January 17, 2002, with 22 claims, four of which are independent (claims 1, 15, 18, and 20). In response to a February 12, 2003 Restriction Requirement, Applicants elected with traverse to pursue claims 1-14 and 19 (Group I).

Pending claims 1-14 and 19 were rejected in a May 22, 2003 Office Action. Applicants responded on October 22, 2003, arguing against the rejections and adding new claims 23-109. Non-elected claims 15-18 and 20-22 were canceled without prejudice solely because of the requirement that they be restricted to another application. They were not canceled for any reason relating to patentability.

In subsequent January 2, 2004, Office Action a majority of the rejections were withdrawn. The rejection of claims 3 and 14 under 35 USC § 112, first paragraph, was withdrawn (January 2, 2004 Office Action, ¶6). The rejection of claims 1,2, 4, 7-8 and 19 under 35 USC § 102(b) over Bodmer *et al.* was withdrawn in view of Applicants' arguments (January 2, 2004 Office Action, ¶8). The rejection of claims 1, 8, 12 and 19 under 35 USC § 102(e) over Morrison *et al.* was withdrawn in view of Applicants' arguments (January 2, 2003 Office Action, ¶8). The rejection of claims 1,2, 4-12 and 19 under 35 USC § 103(a) over Shan *et al.*, Bodmer *et al.*, and Morrison *et al.* was withdrawn in view of Applicants' arguments (January 2, 2004 Office Action, ¶9). The rejection of claims 1,2, 4-13 and 19 under 35 USC § 103(a) over Shan *et al.*, further in view of Bodmer *et al.*, Morrison *et al.*, and Armitage *et al.* was withdrawn in view of Applicants' arguments (January 2, 2004 Office Action, ¶10).

In this Response, Applicants have added new claims 110-142. Claims 1, 2, 4-13, 19, 23-142 are currently pending. The following claims have been amended.

Claim 1 has been amended only to remove a reference to an altered wild-type immunoglobulin hinge region polypeptide that "contains no cysteine residues." This amendment is made to progress prosecution of this case, and Applicants reserve the right to pursue this subject matter in another application. The significance of this amendment is to remove from the claim only a single Markush embodiment. It is not an amendment that alters a remaining claim limitation or impacts any remaining embodiments.

Claim 4 was previously amended to correct claim dependency because it depended from a claim that had been canceled (claim 3). Claim 4 has been amended again to correct language that, by oversight, remained but is unsuitable in light of the fact that it no longer depends from claim 3. Support for the amendment is found throughout the specification including, by way of example, at page 24, last sentence.[1] No change relates to the rejections of this claim under 35 USC 103 or 112, which are disputed in their entirety for reasons set forth below, and no change has been made for any reason related to patentability.

Claims 10 and 11 have been amended to correct the reference to "linker peptide" as used in claim 5. No substantive change has been made and no change has been made for any reason related to patentability.

Claim 23 has been amended to specify that the claimed proteins can lead to ADCC or complement fixation or both. Support for claim 23 is found throughout the specification

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[1] Page 24, last sentence, reads: "In one embodiment of the invention, the mutated hinge region polypeptide is derived from a human IgG wild-type hinge region polypeptide, which may include any of the four human IgG isotype subclasses, IgG1, IgG2, IgG3 or IgG4."

(including the original claims). See, for example, the paragraph bridging pages 10-11, Figures 4, 11, 13, 19 and 20, pages 16, 25, 29, 38, *etc.*, *etc.* Claim 23 has, obviously, not been narrowed nor has it been amended for any reason related to patentability given that there are no art-based rejections of claim 23 and only one rejection under 112 based on the Examiner's question regarding support for the first "wherein" clause following part (d), which has not been amended and is discussed below.

Inclusion in Claim 24 of the term "cell surface receptor" is supported throughout the specification (including the original claims). See, for example, pages 18-22. No change relates to the rejections of this claim under 35 USC 103 or 112, which are disputed in their entirety for reasons set forth below, and no change has been made for any reason related to patentability.

The amendment to claims 24 and 25 regarding the nature of the hinge peptide is supported throughout the specification (including the original claims), as discussed below.

Claim 26 has been amended to correct a typographical error. No substantive change has been made and no change has been made for any reason related to patentability.

Claim 27 has been amended to correct a typographical error that resulted in a multiple dependent claim depending from a multiple dependent claim. No substantive change has been made and no change has been made for any reason related to patentability.

Claims 32-34 have been amended to correct typographical errors. Claims 32 and 33 were also amended to note that they depend from claim 25, which, like claims 32 and 33, references target cells. No substantive change has been made and no change has been made for any reason related to patentability as these alterations have nothing to do with the rejections of these claims under 35 USC 103 or 112, which are disputed in their entirety for reasons set forth below.

Claims 35-38 have been amended to note that they depend from claim 25, which, like claims 35-38, references targets. No change relates to the rejections of any of these claims under 35 USC 103 or 112, which are disputed in their entirety for reasons set forth below, and no change has been made for any reason related to patentability.

Claim 39 has been amended to correct a typographical error that resulted in a multiple dependent claim depending from a multiple dependent claim, and other typographical errors including "are are". Claim 39 has also been amended to indicate that the binding domain is an scFv. No change relates to the rejections of this claim under 35 USC 103 or 112, which are disputed in their entirety for reasons set forth below, and no change has been made for any reason related to patentability.

Claim 42 has been amended to specify dependence from claim 39, with unneeded language thus omitted, in order to correct an error that resulted in a multiple dependent claim depending from a multiple dependent claim. No change has been made for any reason related to patentability.

Claim 43 has been amended to delete unnecessary language, *i.e.*, language that is already present in the claim from which it depends. No change has been made for any reason related to patentability.

Claim 44 has been amended to correct claim dependency. No change has been made for any reason related to patentability.

Claim 46 has been amended to correct a typographical error that resulted in a multiple dependent claim depending from a multiple dependent claim, and to delete unneeded language. No change has been made for any reason related to patentability. The amendment is without prejudice to inclusion of claims directed to non-scFv binding domains in this or another case.

Claim 48 has been amended to correct a typographical error that resulted in a multiple dependent claim depending from a multiple dependent claim, and other typographical errors including "are are". No change has been made for any reason related to patentability. The amendment is without prejudice to inclusion of claims directed to non-scFv binding domains in this or another case.

Claim 49 has been amended to correct the claim dependency and to correct the reference to the hinge peptide of claim 1 to which this claim refers.

Claim 50 has been amended to correct a typographical error that resulted in a multiple dependent claim depending from a multiple dependent claim, a typographical error that led to reference to a "single chain protein" instead of a "protein", and a typographical error in which the word "and" was inadvertently omitted. No change has been made for any reason related to patentability.

Claim 51 has been amended to delete unneeded words and not for any reason related to patentability.

Claim 53 has been amended to correct the claim dependency and to delete unneeded words, and not for any reason related to patentability.

Claim 54 has been amended to delete unneeded words and not for any reason related to patentability.

Claim 55 has been amended to correct the claim dependency and to delete unneeded words and not for any reason related to patentability.

Claim 59 has been amended to correct a typographical error that resulted in a multiple dependent claim. No change has been made for any reason related to patentability

Claim 64 has been amended to note that the single chain protein comprises a single chain Fv capable of binding to a human CD20 and that the hinge peptide is an altered naturally-occurring immunoglobulin hinge region polypeptide. Conforming changes to dependent claims 65-71 have also been made. No change has been made for any reason related to patentability as is clear from the fact that no change relates to the rejections of any of these claims under 35 USC 103 (claims 64-66 only) or 112 (claims 64-71), which are disputed in their entirety for reasons set forth below.

Claims 107 and 108 have been amended to note that the CD20 binding domain is a single chain Fv and that the hinge region polypeptide is an IgE constant hinge region polypeptide. Support for this amendment is discussed below.

Support for new claims 110-142 can be found throughout the originally filed application, including the claims, drawings, and examples, and as set forth above. Without limitation, examples of instances of support in the originally filed specification for various new claims include at least the following: claims 114, 117, 120, 123 and 126 (original claim 9); claim 129 (page 26, first paragraph); and, claims 135 and 136 (page 18, line 13 to page 19, line 2).

Entry of these amendments and new claims is hereby requested. No new matter has been added.

Claim Objections

Applicants thank the Examiner for pointing out the typographical error in claims 32 and 33. In this Response, Applicants have corrected this misprint by changing "capable" to "capable of" in these claims. The scope of the claims have not thereby been narrowed or otherwise altered. Applicant respectfully request that the objections to claims 32 and 33 be withdrawn.

Rejections Maintained

Three rejections from the May 22, 2003 Office Action were maintained by the Examiner in the January 2, 2004 Office Action. Each is addressed in turn below.

35 USC § 112, Second Paragraph

The rejection of claims 1, 2, 4-13, and 19 under 35 USC § 112, second paragraph, as allegedly "indefinite," was maintained, and newly added claim 74 was rejected as well (January 2, 2004 Office Action, ¶11). The Examiner asserted, "the claims require a hinge having, none, one, or two or more cysteines when compared to wild-type, however, the rest of the hinge region is not defined and it is not clear how it is 'derived' from the wild-type hinge region." Applicants again traverse this rejection and respectfully request that this rejection be reconsidered and withdrawn.

As noted at the April 27, 2004 Interview, the word "derived" in claim 1 is read in conjunction with the word "mutated" to refer a sequence difference (for example, a change in the number of cysteine residues by deletion or substitution) or a sequence change made by any means relative to a wild-type hinge region sequence. Thus, in the case of cysteines, for example, the difference or change is relative to the number of cysteine residues normally present in a wild-type hinge region on which the claimed hinge region may be based, or from which it is "derived." Claim 1 is read in light of the specification in which the term "derived" is used on numerous occasions to identify or refer to a difference or change in the number of cysteine residues in a hinge region incorporated into a construct of the invention. See, e.g., page 22, line 26 to page 23, line 10. The specification provides more than sufficient guidance to one skilled in the art with respect to how a "mutated," *i.e.*, different or changed, hinge region having an altered number of cysteines, for example, may be derived from a wild-type hinge region. Further

guidance is provided at page 24, lines 15-26, indicating that a hinge region may be derived from a wild-type hinge region by amino acid substitution or deletion, in this case to alter cysteine residues:

> Similarly, in certain other embodiments of the invention, the binding domain-immunoglobulin fusion protein comprises a binding domain polypeptide that is fused to an immunoglobulin hinge region polypeptide comprising a mutated hinge region polypeptide in which the number of cysteine residues is reduced by amino acid substitution or deletion. A mutated hinge region polypeptide may thus be derived from a wild-type immunoglobulin hinge region that contains one or more cysteine residues. In certain embodiments, a mutated hinge region polypeptide may contain zero or only one cysteine residue, wherein the mutated hinge region polypeptide is derived from a wild type immunoglobulin hinge region that contains, respectively, one or more or two or more cysteine residues. In the mutated hinge region polypeptide, the cysteine residues of the wild-type immunoglobulin hinge region are preferably substituted with amino acids that are incapable of forming a disulfide bond.

The January 2, 2004 Office Action at ¶11 also questions whether the "rest of the hinge region is defined." As noted at the April 27, 2004 Interview, the rest of the hinge region is known as the hinge region is based on or prepared from a wild-type immunoglobulin hinge region.

Applicants respectfully submit that the meaning of the term "derived" is clear and request that the rejections of claims 1, 2, 4-13, 19 and 74 under 35 USC § 112, second paragraph, be reconsidered and withdrawn.

35 USC § 102

Claims 1, 2, 5, 7-11, 19 and newly added claims 24-28, 31-34, 39, 50-51, 59, 72-74, 78, 82, 84-87, 93-94, 97 and 98 stand rejected under 35 USC § 102(b) as allegedly anticipated by Shan *et al.*, "Characterization of scFv-Ig Constructs Generated from the Anti-CD20 mAb 1F5 Using Linker Peptides of Varying Lengths," *Journal of Immunology* **162**:6589-6595, 1999 (January 2, 2004 Office Action, ¶12).

The Office Action opines that Shan *et al.* teaches the claimed molecules "and just because they do not mention the inherent properties does not mean the compound does not have the property" (January 2, 2004 Office Action, ¶12). As noted at the Interview with the Examiner on April 27, 2004, it believed that this concept confounds the properties of a compound with its utilities, a conclusion of anticipation by inherency requiring a determination of inevitability.[2]

A biotechnology start-up company owns this application. Despite the difference of opinion between Applicants and the PTO on the question of lack of inherency, Applicants have amended claim 1 in order to progress prosecution of this case. Shan *et al.* references a hinge that has zero cysteine residues. Applicants have removed clause (i) from part (a) of independent claim 1 which references a hinge "that contains no cysteine residues." It is understood and agreed with the Patent Office that the significance of this amendment is to remove from the claim only a single embodiment, that it is not an amendment that alters a remaining claim limitation or impacts any remaining embodiments, and that, accordingly, *Festo* has no applicability and the Doctrine of Equivalents is fully applicable to all aspects of the claim as amended.

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[2] See page 29 of Applicants' October 22, 2003 Response, stating, in part, "Indeed, with regard to potential uses of the 1F5 scFv-Ig constructs, the Shan *et al.* concluded only that (1) apoptosis may be induced as a result of antigen binding by the scFv portion of the molecule (though optimal apoptosis required cross-linking with a second antibody) and that (2) therapy of CD20-expressing B cell malignancies with 1F5 scFv-Ig "radionuclide conjugates" merit further investigation. However, radionuclide conjugation as suggested by Shan *et al.* with regard to use of the scFv constructs, would not be expected to necessarily preserve ADCC and CDC activities. For example, there are exposed aromatic residues in the CH2 and CH3 domains that are thought to be involved in C1q complement binding (Isenman *et al.*, *Biochemistry* 16:233-240 (1977)) that may be derivatized during an oxidative iodine radiolabeling procedure using chloramine T or iodogen. Although alternative methods of radiolabeling by conjugation of amino groups on lysine residues have been published (Smellie *et al.*, *Cancer Res.* 55:5842s-5846s (1995)), these procedures may also affect ADCC and CDC functions by causing conformational changes and altering residues involved in binding to Fc receptors and to complement components. For example, lysines 320 and 322 of the CH2 domain have been shown to be components of the C1q binding site on IgG (Duncan and Winter, *Nature* 322:738-740 (1988)) and lysine 322 was reported to be required for CDC activity of recombinant human IgG3 antibodies (Thommesen *et al.*, *Mol. Immunol.* 37:995-1004 (2000))."

Applicants respectfully request that the rejection of claims 1, 2, 5, 7-11, 19, 24-28, 31-34, 39, 50-51, 59, 72-74, 78, 82, 84-87, 93-94, 97 and 98 under 35 USC § 102(b) be reconsidered and withdrawn.

35 USC § 103

Claims 1, 2, 4-11, 19 and newly added claims 24-28, 31-34, 39, 50-51, 59, 72-74, 78, 82, 84-87, 93-94, 97 and 98 stand rejected under 35 USC § 103(a) as allegedly being unpatentable over Shan *et al.* in view of Bodmer *et al.* The Office Action states, "This rejection has been altered and Bodmer is only needed to make up for the teachings lacking in Shan of a human variable region" (January 2, 2004 Office Action, ¶13).

Shan *et al.* has numerous shortcomings. It does not, for example, suggest or teach constructs having a hinge containing one cysteine residue, a human IgA hinge, a human IgA hinge region polypeptide with no cysteine residues, or a human IgA hinge containing one cysteine residue, all of which are set forth, for example, in claim 1. Thus, it cannot support a *prima facie* case under §103.

Notwithstanding the deficiencies of Shan *et al.*, Bodmer *et al.* does not complete a *prima facie* case. In addition to its inadequacies, it is not properly combinable with Shan *et al.*

Bodmer *et al.* is directed to complete antibodies and $(Fab')_2$ fragments. Bodmer *et al.* fails to teach or suggest a single chain Fv. Bodmer *et al.* fails to teach or suggest an immunoglobulin without a CH1 domain. There is no suggestion that provides a basis for combining Shan *et al.* and Bodmer *et al.* Accordingly, Applicant respectfully request that the rejection of claims 1, 2, 4-11, 19, 24-28, 31-34, 39, 50-51, 59, 72-74, 78, 82, 84-87, 93-94, 97 and 98 under 35 USC § 103(a) over Shan *et al.* in further view of Bodmer *et al.* be reconsidered and withdrawn.

Applicants also note that Shan *et al.* is only directed to molecules that include an IgG1 hinge with three serine residues in place of three cysteine residues. However, Applicants' pending claims 1, 2, 4-11, 19, 24-28, 31-34, 39, 50-51, 59, 72-74, 78, 82, 84-87, 93-94, 97 and 98 do not include constructs containing an IgG1 hinge with three serine residues in place of three cysteine residues. Thus, even if, for the purpose of analyzing the merits of this rejection, one were to hypothetically combine Shan *et al.* and Bodmer *et al.*, it is seen that the combination would not yield an anti-CD20 construct within the claims and the rejection therefore cannot stand. *See CFMT, Inc. v. Yieldup International Corp*, 349 F.3d 1333, 1342, 68 USPQ2d 1940, 1947 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985, 180 USPQ 580, 583 (CCPA 1974) (obviousness requires a suggestion of all limitations in a claim)).

New Grounds of Rejection

35 USC § 112, First Paragraph

1) In paragraph 15 of the January 2, 2004 Office Action, claims 52-53 and 55-59 were rejected under 35 USC § 112, first paragraph. The Examiner questioned whether "the claimed biological materials are (1) known and readily availably to the public; (2) reproducible from the written description," stating that it was not clear whether "a cell line which produces single chain antibody having the exact chemical identity of L6, HD37, or G28-1 is known and publicly available, or can be reproducibly isolated without under experimentation." The Examiner noted that a deposit of biological materials may be made.

Applicants respectfully traverse this rejection. Regarding 2H7, the Examiner stated, "Deposit of antibody 2H7 is not needed because the specification teaches the variable light and heavy chain amino acid sequence for the single chain antibody (see Figure 1)" (January 2, 2004 Office Action, pages 8-9). Similarly, there is no 112 or deposit issue regarding antibody L6,

antibody G28-1, or antibody HD37. The rejection must be reversed because, *inter alia*, the light chain variable domain and heavy chain variable domain sequences for L6, HD37, and G28-1 type proteins are either provided in the instant application or were known and readily available in the public domain before the application was filed.[3]

Heavy chain variable domain sequences for an L6 anti-carcinoma mAb were published in U.S. Patent No. 5,354,847, issued October 11, 1994 to Liu *et al.* for "Chimeric antibody with specificity to human tumor antigen." Additionally, an L6 cell line is publicly available (see, e.g., HB 8677 deposited with the ATCC on Dec. 6, 1984). See claim 1 of the '847 patent.

The light chain variable domain and heavy chain variable domain sequences for mouse anti-human G28-1 (which binds to CD37) are provided in SEQ ID NO:9, and the sequence for a mouse anti-human CD37 single chain fv is provided in SEQ ID NO:13. This sequence and the information provided in Example 1 with respect to the construction of single chain Fvs may be used by one of skill in the art to make a G28-1 single chain Fv without undue burden.

The instant application also provides the light chain variable domain and heavy chain variable domain sequences for mouse anti-human CD19 (HD37) in SEQ ID NO:8.

Given the availability of these sequences, *inter alia*, Applicants submit that a deposit of biological materials is not necessary and respectfully request that the rejections of claims 52-53 and 55-59 under 35 USC § 112, first paragraph, be reconsidered and withdrawn.

2) In paragraph 16 of the January 2, 2004 Office Action, claims 23 and 26-109 were rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action stated that the Examiner was unable to locate

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[3] *See* 37 C.F.R § 1.802(b) ("Biological material need not be deposited, *inter alia*, if it is known and readily available to the public or can be made or isolated without undue experimentation."); MPEP § 2404.02 ("No deposit is required . . . where the required biological materials can be obtained from publicly available material with only

support for part (d) of claim 23 in the specification at the locations specified by Applicants in their response to the May 22, 2003 Office Action. It was confirmed at the April 26, 2004 Interview that this rejection pertained to the first "wherein" clause of claim 23, which states:

> wherein said hinge peptide is an IgG or IgA hinge peptide that contains one or two cysteine residues, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally-occurring IgG or IgA antibody is not deleted or substituted with an amino acid.

The Examiner requested clarification of the written description support for this clause.

The application as filed provides clear support for this wherein clause. The use of modified IgG and IgA hinge peptides having one cysteine residue is discussed throughout the specification and original claims. See, for example, claim 1 and pages 11, 23-24, 37, *etc.* The specification also provides support for modified IgG and IgA hinge peptides having two cysteine residues. For example, as noted at the Interview, the specification states, "Similarly, in certain other embodiments of the invention, the binding domain-immunoglobulin fusion protein comprises a binding domain polypeptide that is fused to an immunoglobulin hinge region polypeptide comprising a mutated hinge region polypeptide in which the number of cysteine residues is reduced by amino acid substitution or deletion" (page 24, lines 15-19, of the originally filed application). The wherein clause refers to IgA hinges, all of which have three cysteines. It would thus be clear to one skilled in the art that such hinge regions "in which the number of cysteine residues is reduced" could therefore have zero, one or two cysteines. See also page 29 of the specification, which refers to the deletion or substitution of only one cysteine residue, in that case the "Cys residue of the hinge which makes a disulfide bond with a

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routine experimentation and a reliable screening test" (citing *Tabuchi v. Nubel*, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977); and *Ex Parte Hata*, 6 USPQ2d 1652 (Bd. Pat. App. & Int. 1987)).

corresponding Cys of the light chain."[4] A similar analysis is applicable to IgG1 hinge peptides that are known to contain three cysteines, as well as to the other IgG hinge peptides that contain two (IgG4), four (IgG2), or eleven (IgG3), cysteines.

Applicants submit that written description support for this wherein clause referencing hinges containing one or two cysteines, is clear, and Applicants respectfully request that the rejection under 35 USC § 112, first paragraph, of claims 23 and claims 26-109 be reconsidered and withdrawn.

3) In paragraph 17 of the January 2, 2004 Office Action, claim 53 was rejected under 35 USC § 112, first paragraph, on the allegation that is does not "comply with the written description requirement." Claim 53 reads as follows:

> A pharmaceutical composition of claim 52 wherein said single chain protein target is CD20 and said single chain Fv is capable of binding CD20, wherein said single chain Fv is not a 1F5 single chain Fv.

Noting that he was unable to find support for the limitation, "wherein said single chain Fv is not a 1F5 single chain Fv," the Examiner requested that Applicants "provide specific support for the limitation in the specification as originally filed or remove it from the claim" (January 2, 2004 Office Action, ¶17).

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[4] The specification at page 29, lines 4-19, reads (emphasis added):

"The nucleotide sequences encoding the variable regions of the heavy and light chains, joined by a sequence encoding a linker, are joined to a nucleotide sequence encoding antibody constant regions. The constant regions are those which permit the resulting polypeptide to form interchain disulfide bonds to form a dimer, and which contain desired effector functions, such as the ability to mediate antibody-dependent cellular cytotoxicity (ADCC). For an immunoglobulin-like molecule of the invention which is intended for use in humans, the constant regions will typically be substantially human to minimize a potential anti-human immune response and to provide approbate effector functions. . . . In preferred embodiments, the CH1 domain is deleted and the carboxyl end of the second variable region is joined to the amino terminus of CH2 through the hinge region. The Cys residue of the hinge which makes a disulfide bond with a corresponding Cys of the light chain, to hold the heavy and light chains of the native antibody molecule, can be deleted or, preferably, is substituted with, *e.g.*, a Pro residue or the like."

In order to meet the burden of establishing a *prima facie* case, the Patent Office is required to explain why one of ordinary skill in the art would not recognize that the applicants invented the subject matter they now claim. Merely positing that the specification did not expressly state the negative limitation does not meet this burden. *Ex parte Parks*, 30 U.S.PQ.2d 1234, 1236 (Bd. Pat. App. & Inter. 1993). *See also In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984) ("It is not necessary that the claimed subject matter be described identically [in the written description])." The Patent Office has not met this burden. Accordingly, the rejection must be withdrawn.

Notwithstanding the lack of a *prima facie* case, support for claim 53 is found throughout the specification as originally filed. Various different single chain Fv choices are mentioned in the specification. A broad class is identified as embracing suitable choices for a single chain Fv and single chain Fv targets. See, for example, pages 12, 18-22, and 27-29. Examples of particular single chain Fvs are found throughout the specification, including 2H7 single chain Fvs,[5] HD37 single chain Fvs,[6] L6 single chain Fvs,[7] and G28-1 single chain Fvs.[8]

The 1F5 single chain Fv that is the subject of the claim 53 proviso is also referred to in the specification. For example, 1F5 murine monoclonal antibodies which specifically bind CD20 were used in Example 3 of the instant application (page 70, lines 16-26). Amended claim 53 excludes binding domain-immunoglobulin fusion proteins which comprise the light chain

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[5] See, e.g., Figure 7 (2H7scFv-CD154 L2 and 2H7scFv-CD154-S4), Figure 8 (2H7scFv-154), Figure 9 (2H7scFv-154), and Example 1 (cloning of 2H7 variable region), Example 2 (expression of 2H7sv) and Example 4 (2H7 CD154 fusion proteins).

[6] See, e.g., Figures 17-19 and Example 7.

[7] See, e.g., Figures 20 and 21 and Example 8.

[8] See, e.g., Figures 19, 22 and 23 and Example 9.

variable regions and heavy chain variable regions of the 1F5 monoclonal antibodies described in Example 3.

This proviso is explicitly permitted by the MPEP § 2173.05 ("Negative Limitations"), which cites *In re* Johnson, 558 F.2d 1008, 194 USPQ 187 (CCPA 1977) in support.[9] The circumstances of the present rejection are analogous to those in *Johnson*, where the claim read:

> A substantially linear thermoplastic polyarylene polyether composed of recurring units having the general formula:
>
> -(O-E-O-E')-
>
> where E is the residuum of a dihydric phenol and E' is the residuum of a benzenoid compound having an inert electron withdrawing group in one or more of the positions ortho and para to the valence bonds having a sigma value about 0.7, and where both of said residuum (sic, residua) are valently bonded to the ether oxygens through aromatic carbon atoms with the provisos that E and E' may not both include a divalent sulfone group and may not both include a divalent carbonyl group linking two aromatic nuclei.

The first proviso excluded the species of a lost count in an interference, and the second proviso was analogous or equivalent to the first species. 558 F.2d at 1013. The Board decided that "no antecedent basis exists in the parent case" for the "limited genus" in the claim at issue. 558 F.2d at 1018. On appeal, the CCPA reversed, stating the only inquiry to be "whether, after exclusion from the original claims of two species specifically disclosed in the 1963 application, the 1963 disclosure satisfies section 112, first paragraph for the 'limited genus' now claimed." 558 F.2d at 1017-1018.

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[9] MPEP 2173.05(i) reads (emphasis added):

"Any negative limitation or exclusionary proviso must have basis in the original disclosure. If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims. See *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) ("[the] specification, having described the whole, necessarily described the part remaining."). See also *Ex parte Grasselli*, 231 USPQ 393 (Bd. App. 1983), *aff'd mem.*, 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. Note that a lack of literal basis in the specification for a negative limitation may not be sufficient to establish a *prima facie* case for lack of descriptive support. *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. & Inter. 1993)."

The CCPA found "more than ample basis for the claims of such scope," noting that "specific choices are mentioned for the E precursor compound, a broad class is identified as embracing suitable choices for the E' precursor compound, and twenty-six 'examples' are disclosed which detail fifteen species of polyarylene polyethers." Only fourteen of those species and twenty-three of the "examples" were within the scope of the claims on appeal.

Two of the various choices for E and E' precursor compounds were deleted from the protection sought, because, as the court noted, "appellant is claiming less than the full scope of his disclosure." According to the *Johnson* court, "It is for the inventor to decide what bounds of protection he will seek." The court specifically held that to deny appellants the benefit of their application would "let form triumph over substance, substantially eliminating the right of an applicant to retreat to an otherwise patentable species merely because he erroneously thought he was first with the genus when he filed." 558 F.2d at 1018.

Here, similarly, there is no question but that Applicants' specification "satisfies section 112, first paragraph for the 'limited genus' now claimed." Only one of the many choices for a single chain Fv has been deleted from the scope of claim 53. As the court held in *In re Johnson*:

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute.

I558 F.2d at 1019.

Applicants respectfully request that the rejection under 35 USC § 112, first paragraph, of claim 53 reconsidered and withdrawn.

4) In paragraph 18 of the January 2, 2004 Office Action, claims 107 and 108 were rejected under 35 USC § 112, first paragraph. Claim 107 refers to a single chain protein comprising a binding domain polypeptide capable of binding to CD20 joined to an IgE constant region polypeptide, and claim 108 specifies that the claim 107 protein comprises two or three IgE constant region domains. Claims 107 and 108 and amended claims 107 and 108 are supported by the specification as filed, which refers to the use of "any hinge peptide or polypeptide that occurs naturally" (see, e.g., paragraph bridging pages 22 and 23). This includes the IgE hinge, which is known and understood to constitute the IgE CH2 constant region. Applicants request that the rejections of claims 107 and 108 under 35 USC § 112, first paragraph, be withdrawn.

35 USC § 103

Claims 1, 2, 4-11, 19 and newly added claims 24-39, 50-51, 59-66, 72-74, 78, 82, 84-87, 93-94, 97, 98, 106 and 109 were rejected under 35 USC § 103(a) as allegedly unpatentable over Shan *et al.* in view of Kucherlapati *et al.*, U.S. Patent No. 6,150,584 (January 2, 2004 Office Action, ¶19). The Office Action alleges that "Kucherlapati *et al.* teach human antibodies to a wide range of therapeutic antigens which are CD's, interleukins, tumor antigens, etc (see column 9-11)." Without further discussion, the Office Action concludes that Kucherlapati *et al.* provides motivation and a reasonable expectation of success to produce constructs "as taught by Shan that bound the antigens taught by Kucherlapati et al. because Shan et al. teach that teach that the human IgG1 hinge, CH2, CH3 was used to facilitate purification and the hinge was modified to produce monomeric scFv-Ig molecules." Applicants respectfully traverse this rejection.

Shan *et al.* is discussed above and in Applicants' previous Office Action Response. As noted by the Examiner, Shan *et al.* cannot support a *prima facie* case of unpatentability under §103.

Kucherlapati *et al.* cannot complete the *prima facie* case. Kucherlapati *et al.*, entitled "Human Antibodies Derived from Immunized Xenomice," relates to the production of human antibodies in transgenic mice. It lists "large numbers of antigens for which human antibodies and their human analogs would be made available by the methods of the invention" (columns 9-10). The patent contains twelve claims, seven to transgenic mice and five to methods of producing "a fully human IgG antibody" using the transgenic mice.

There is no basis for combining the technical disclosures of these two documents -- one being directed to examination of linker length in scFvs "to assess the relative merits of scFvs compared with intact anti-CD20 Abs" (page 6589, col. 2) and the other being directed to methods for producing human antibodies in mice -- and the Patent Office has not provided one.

"To establish a *prima facie* case, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference or references, when combined, must teach or suggest all the claim limitations. MPEP 706.02(j), citing, *In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991) (emphasis added).

The Kucherlapati *et al.* list of antigens in columns 9-10 relates to "human antibodies" that allegedly can be made by using the genetically engineered mice described and claimed in the patent. Kucherlapati *et al.* does not specifically relate to single chain Fvs. It says nothing about single chain Fvs-containing constructs. Columns 9-10 contain no statement or suggestion about

making or using an scFv capable of binding any of the listed antigens. Additionally, there is no teaching of a specific scFv construct in Kucherlapati *et al.*, let alone any specific teaching of a single chain Fv binding domain construct capable of binding any of the antigens listed in the Kucherlapati *et al.* patent.

Applicants further note that the application for the Kucherlapati *et al.* patent was filed in 1996, eight years ago, and that the patent issued on November 21, 2000, nearly four years ago. No rush to combine the disclosures of Shan *et al.* article and the Kucherlapati *et al.* patent is apparent in the literature. This evidences either the lack of a suggestion or motivation to do so, the lack of a reasonable expectation of success, or both. This represents objective evidence of nonobviousness. Applicant's respectfully submit that there is no prima facie case under 103 and request that the rejection of claims 1,2, 4-11, 19, 24-39, 50-51, 59-66, 72-74, 78, 82, 84-87, 93-94, 97, 98, 106 and 109 under 35 USC § 103(a) as allegedly being unpatentable over Shan *et al.* in further view of Kucherlapati *et al.* (U.S. Patent No. 6,150,584) be reconsidered and withdrawn.

Applicants also note the lack of a *prima facie* case for an additional reason. Shan *et al.* is only directed to molecules that include a hinge with serine residues in place of all cysteine residues. Applicants' pending claims, however, do not include constructs containing an immunoglobulin hinge with serine residues in place of all cysteine residues.

CONCLUSION

Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted

Ledbetter *et al.*

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